# Leukotriene C4 Detection as an Early Graft Function Marker in Liver Transplantation

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Leukotrienes are a group of compounds belonging to the eicosanoid family that are formed from the metabolism of arachidonic acid by means of 5-lipoxigenase. Leukotriene C4 (LTC4) has a pronounced proinflammatory character and is formed by combining leukotriene A4 with glutation. This step is catalyzed mainly by the isoenzyme 4-4 of the hepatic glutation transferases,[1] although other enzymes may participate in its formation.[2,3] The liver plays a decisive part in the formation of this compound despite the fact that it can be synthesized along other cellular lines. In orthotopic liver transplant (OLT), the evaluation of the early functioning of the graft is, in many cases, complex. The difficulty of evaluation lies in the absence of specific markers to indicate (1) when the transplanted organ will prove viable notwithstanding the damage resulting from preservation, and (2) when these lesions are irreversible. The aim of this study is to determine whether there is a relationship between the ability to synthesize LTC4 immediately after OLT and the early functioning of the graft.

## MATERIALS AND METHODS

Fifteen orthotopic liver allotransplants were performed on cross-bred dogs weighing between 20 and 30 kg. The technique de-scribed by Starzl et al[4-6] was applied, with a few modifications. Euro-Collins solution was used for preservation, with a mean cold ischemia time of 93 ± 22 minutes. The animals were divided into two groups: In group I (n = 5) the preservation solution was used at 4°C, and in group II (n = 10) a preservation defect was caused by using the Euro-Collins solution at between 10° and 15°C.

During the anhepatic phase, a femoro-porto-jugular bypass was performed with spontaneous flow. Afterward, the venous anastomoses were performed in the following order: suprahepatic cava, infrahepatic cava, and porta. After revascularizing

the portal vein system, end-to-end arterial anastomosis was performed between the celiac axis of the donor and recipient. In some animals, this anastomosis is performed end-to-side between the hepatic artery of the donor and the exit of the celiac axis of the recipient. Reconstruction of the gallbladder was performed by means of cholecystoduodenostomy. In all cases, the animals were given an autotransfusion of blood extracted a week before the operation. None of the animals was given immunosuppressives.

Blood tests were taken at the following points during the study: 1 week before the operation, after the endotracheal intubation before commencing the laparotomy, 15 minutes after beginning the anhepatic stage, and then 5 minutes, 15 minutes, 1 hour, 3 hours, 8 hours, and 24 hours after the graft had been revascularized through the portal veins.

At all these points, tests measured glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), prothrombin time, fibrinogen, lactic acid, and LTC4.

Tests for LTC4 were performed by radioimmunoassay. Anti-body anti-LTC4 was a gift from Merck Frosst (Montreal, Canada).

## RESULTS

The average survival for group I was 6.6 days (range 4 to 8), whereas all the animals of group II died in the first 24 hours with generalized hemoperitoneum; microscopic studies confirmed severe ischemic lesion of the liver in every case in this group.

Figure 1 shows the levels of LTC4 in both groups. In group I, LTC4 was detected in all the animals immediately after revascularization, and the curve shows that levels were rising during the immediate postoperative period. In group II, no LTC4 was found in any of the animals after the anhepatic phase. The parameters calculated for graft viability are shown in Table 1.

## DISCUSSION

Evaluation of early graft function in liver transplantation is often hindered by the absence of a specific marker to determine the degree of viability. The parameters that are generally used to assess graft functionality (GOT, GPT, bilirubin, alcaline phosphatase, prothrombin time, fibrinogen, and lactic acid) are not sensitive enough to measure the extent to which preservation damage can be reversed. Various clinical and experimental studies have recently brought the energy status of the preserved liver into relation with the graft's viability. [7,8] Other studies relate the early functioning of the graft with its ability to clear various substances, such as bile acids, endotoxins, amino acids, and hyaluronic acid.[9-12]

In our study, the absence of LTC4 from peripheral blood after revascularization is related in all cases to reduced graft viability, which is probably due to the liver' s inability to perform glutation and/or enzyme synthesis. By contrast, LTC4 was detected in all the viable grafts immediately after revascularization. The capacity for synthesizing LTC4 may prove a good marker for early liver graft function.

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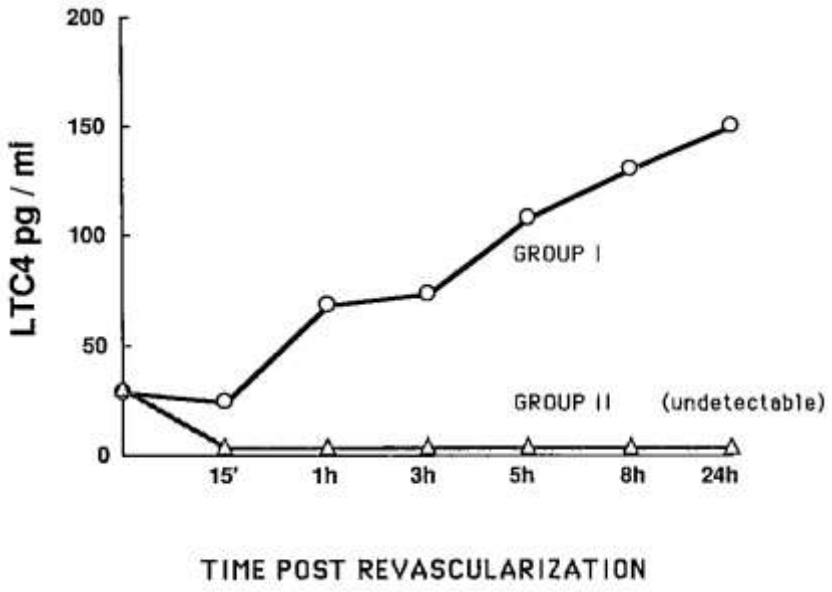


**Figure 1.** Levels of LTC4

| **Table 1.** Parameters Calculated for Graft Viability | | | | |
|---|---|---|---|---|
| | Time Postrevascularization | | | |
| | **3 h** | | **24 h** | |
| | **Group I** | **Group II** | **Group I** | **Group II** |
| GOT | 1408 ± 622 | 2648 ± 1211 | 1264 ± 483 | 7211 ± 1695 |
| GPT | 1280 ± 579 | 2640 ± 1541 | 1311 ± 517 | 8037 ± 1831 |
| Lactic acid | 7.1 ± 1.8 | 8.9 ± 2.1 | 4.6 ± 2.3 | 18.2 ± 3.1 |
| Fibrinogen | 103 ± 48 | 39 ± 12 | 219 ± 54 | 41 ± 13 |